Editorial

Cost-Effectiveness of Genotyping in Inherited Arrhythmia Syndromes

Are We Getting Value for the Money?

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Over the last decade, the identification of the diverse genetic basis of most important inherited arrhythmia syndromes has remarkably changed our attitude toward these life-threatening diseases. Just over 10 years ago, long-QT syndrome (LQTS) was considered one disease entity, Brugada syndrome (BrS) had just been described, and short-QT syndrome was not yet recognized. In addition to improved understanding of the pathophysiological basis of these disorders, these advances have added genetic testing to our diagnostic armamentarium, providing new opportunities for patient management. Early (presymptomatic) identification and treatment of patients at risk of developing fatal arrhythmias is now a reality. More importantly, in particular in LQTS, gene-specific aspects of disease management have evolved, making gene testing highly desirable.1

First, it should be noted that getting to a genetic diagnosis is not equivalent to ordering a “Familion test.” Genetic counseling is inextricably connected to obtaining the molecular genetic testing, and the associated costs (also significant) should therefore be considered an inherent part of the process. In addition, as presymptomatic testing (ie, genetic testing and cardiologic evaluation) has significant psychological impact,3,4 it cannot be emphasized enough that (cardio-) genetic testing requires a concerted action of dedicated cardiologists, clinical geneticists, and social workers. Furthermore, the mere fact that almost half of the patients referred to the Mayo Clinics for LQTS (genetic) testing did not have LQTS6 emphasizes that these tests are best ordered/coordinated by dedicated “cardiogeneticists,” be it either with a cardio-logic or genetic background. Clearly, these factors will increase costs, particularly in those cases that are straightforward.

On the other hand, costs may be reduced by a skilled team that uses targeted genotyping based on phenotype. In BrS and catecholaminergic polymorphic ventricular tachycardia (CPVT), the costs for genotyping are relatively fixed, although still highly variable between countries, because only 1 gene is screened. However, careful phenotyping makes a large difference in these syndromes; in both BrS and CPVT, the yield was significantly higher in “conclusive” cases compared with “possible” cases.2 In BrS, the presence of atrioventricular block, which is known to be associated with SCN5a involvement,6 further increases the yield from 13% to 23%. In LQTS, one may postulate that using all clinically available information could efficiently target genotyping and thereby reduce costs. Indeed, in a small prospective study, we were able to demonstrate that it makes sense to use the available genotype-specific information.7 Forty patients with a conclusive diagnosis of LQTS were subject to molecular genetic testing. In 28 of 31 successfully genotyped patients, the putative, causative gene was correctly predicted.7 This compared with 18 of 31 cases in which the first step was screening for KCNH2, the most prevalent gene in the Dutch population.7 Predicted costs of screening the 5 LQTS genes, also available on the Familion LQTS test, would be €3871 ($4839) per successfully genotyped patient ($40×3000)/31; Dutch prices, ±€600 per gene), whereas targeted screening based on phenotypic information would bring that number down to €1587 ($1984).

A drawback of targeted testing is that double mutations will be missed. The prevalence of these is estimated to be between 5% and 10%, as was also the case in the present study (7%).2 The impact of double mutations on counseling strategies is not well studied, but it can be predicted that not

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every identified variant will have a similar impact (as discussed later). The identification of a causative mutation in a proband with either disease enables presymptomatic identification and timely treatment of family members. Because disease penetrance is by no means complete in either syndrome, genetic testing is the only way to conclusively identify carriers. This is a major argument for genetic testing, and in conclusive cases of LQTS, CPVT, and conduction disease-associated BrS, the costs seem acceptable. In addition, confirmation of a known mutation at low cost would favorably influence genotyping costs per family. In suspected cases, with considerable higher genotyping costs, the authors argue that knowing the genotype is more important in LQTS, because of its impact on disease management, compared with the other diseases.\(^2\) This seems to be the case for SCN5a-related LQTS (LQTS3),\(^1\) although recent studies in large LQTS cohorts also suggest a genotype-specific risk within 1 gene.\(^8\) With current costs in mind, one could argue that, for the moment, exclusion of SCN5a is a cost-effective approach in suspected (not conclusive) cases.

Molecular genetic testing proved to be very inefficient and costly in cardiac arrest survivors without a clear phenotype (idiopathic ventricular fibrillation) and in family members of deceased young patients. The authors note that genetic screening is often the “last hope” to establish the cause of death is not a good reason to order these tests. In the idiopathic ventricular fibrillation group, we have to await the identification of new genes, but a more extended evaluation than accepted by the authors also seems mandatory (eg, additional epinephrine or isoproterenol challenge to unmask CPVT). In the latter group, a thorough clinical evaluation of all available close family members is recommended before genetic testing, because it has been shown that a clinical diagnosis, which could direct genetic testing, is achieved in 40% to 50% of families.\(^9,10\) We doubt whether the authors’ recommendation to screen RyR2 in cases with catecholaminergic-related events (costs per positive genotype of $21 560!) would still stand when it is performed in idiopathic ventricular fibrillation probands who have a negative adrenergic challenge or in families with negative family screening. It is likely that the earlier discussion on costs of genotyping will soon be outdated. “Cardiochips” are already in place for hypertrophic cardiomyopathy,\(^11\) and it is a matter of time before these uniform gene arrays are available for primary arrhythmia syndromes (the “Sudden Cardiac Death DNA array”). A little further down the road is whole-genome sequencing (the $1000 genome scan!), an unbiased approach, potentially to be used in every proband. It is likely that this approach will render current screening methods irrelevant. Regardless of the approach chosen (unbiased or targeted screening), however, is the interpretation of the clinical significance of the genetic variants that are identified. For diseases that predispose to sudden death, interpretation of genetic tests is critical, and unfortunately, it is becoming increasingly clear that it is not always straightforward to distinguish a pathogenic variant from an innocuous background variant. In LQTS, BrS, and CPVT, the majority of identified “mutations” are novel missense mutations. Extensive genotyping studies (SCN5a and relevant potassium channel genes) in so-called healthy controls revealed a ±5% yield of novel, rare, missense mutations with <0.5% allelic frequency that are not all likely to be pathogenic.\(^12,13\) Hence, the identification of a rare missense mutation is no proof for pathogeneity, and false-positives will occur. Altogether, the data provided support a strong plea for more available, general, and reimbursed genetic testing. The heterogeneous pathophysiological character of the variety of genetic arrhythmia syndromes precludes uniform treatment. Information as to the specific genetic basis is becoming critical, as is most clear now in LQTS. Importantly, an appropriate counseling strategy should be an inherent part of all genotyping efforts. To increase the yield of genetic testing, it is the responsibility of involved physicians to phenotype as completely as possible. Subsequent targeted genetic testing could significantly reduce genotyping costs. Unbiased whole-genome genotyping at low costs seems around the corner but may yet be a couple of years in the future. It is important to note, however, that current as well as future genetic testing strategies, with an avalanche of sequencing data, demand that much more effort be devoted to developing methods that facilitate correct interpretation of the molecular genetic results. In particular, in inherited diseases associated with sudden death at a young age, neither a false-positive nor a false-negative molecular misdiagnosis is affordable.

Disclosures

None.

References


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